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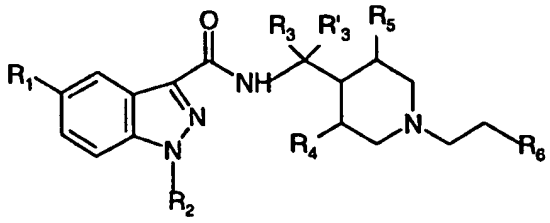

(I)

(57) Abstract

A compound having general formula (I) wherein R_1, R_2, R_3, R'_3, R_4, R_5 and R_6 have the meanings stated in the description, acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

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"Indazole amide compounds as serotoninergic agents"

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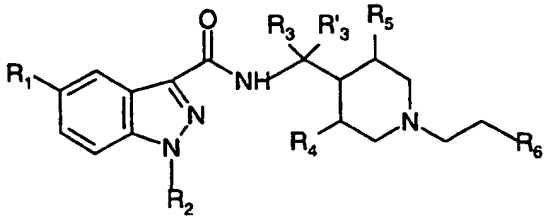
The present invention relates to an indazole amide compound possessing a serotoninergic action, a method for preparing thereof and the pharmaceutical compositions containing the same.

Amongst the numerous known families of serotonin receptors, the $5HT_4$ receptors have only recently been identified in the urinary bladder, smooth and cardiac muscle and specific areas of the central nervous system. Compounds possessing agonistic, partially agonistic and antagonistic actions against such receptors are of potential interest in pharmacological treatment of disorders of gastrointestinal motility, disorders of the central nervous system, urinary incontinence and cardiac arrhythmia. The action of such compounds in fact takes place by mimicking or antagonising the ability of serotonin to stimulate intestinal motility by activation of the enteric neurons, to modulate important cerebral processes such as training, memory and anxiety, to induce relaxation of the urinary bladder and to increase frequency of atrial contraction.

A family of indazole amide compounds has now been found which possess affinity with $5HT_4$ receptors and which act as partial agonists or antagonists of serotonin.

It is therefore a first object of the present invention to provide an indazole amide compound having the general formula:



(I)

wherein

R_1 is hydrogen;

R_2 is isopropyl;

R_3 and R'_3 are hydrogen;

R_4 and R_5 are hydrogen;

R_6 is selected from the group comprising C_{1-3} alkyl, C_{3-7} cycloalkyl, heterocyclic ring having from 5 to 6 members where 1 to 4 members are heteroatoms, the same or different from each other, selected from the group comprising N, O and S, dimethylamino C_{1-3} alkyl, methoxy C_{1-3} alkyl, N-phenyl amide, aminosulphonylmethyl, dihydroxy C_{2-3} alkyl, aryl, aryl substituted by at least a group selected from halogen and hydroxy, aryl C_{1-3} alkyl;

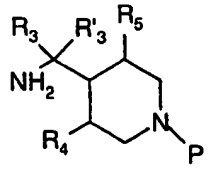
acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

Preferred examples of aryl are phenyl, naphthyl and biphenyl.

Preferred examples of heterocyclic rings are thienyl, furanyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furazanyl, pyrrolinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, morpholinyl, triazinyl, thiazolyl, tetrazolyl and thiadiazolyl. Typical examples of R_6 are cyclopropyl, cyclohexyl, pyridinyl, tetrazolyl, morpholinyl, methoxymethyl, methoxypropyl, phenyl, chlorophenyl, bromophenyl, hydroxyphenyl, phenethyl, dimethylaminomethyl, and aminosulphonylmethyl.

It is a second object of the present invention to provide a process for preparing a compound of the formula (I), acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof, comprising:

a) acylating a 4-aminomethyl piperidine of the formula:



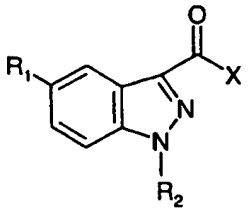
(II)

wherein

R_3, R'_3, R_4 and R_5 have the above mentioned meanings, and

P is a suitable protecting group;

by means of a 1-alkyl-indazole-3-carboxylic acid halide of the formula:



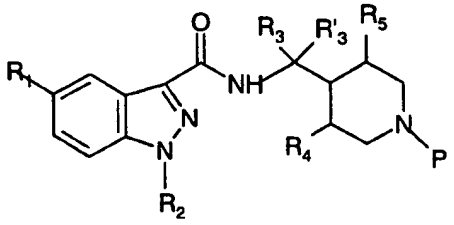
(III)

wherein

R_1 and R_2 have the above mentioned meanings, and

X is halogen,

to give a compound of the formula:

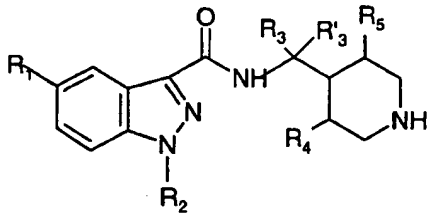


(IV)

wherein

R_1, R_2, R_3, R'_3, R_4, R_5 and P have the above mentioned meanings,

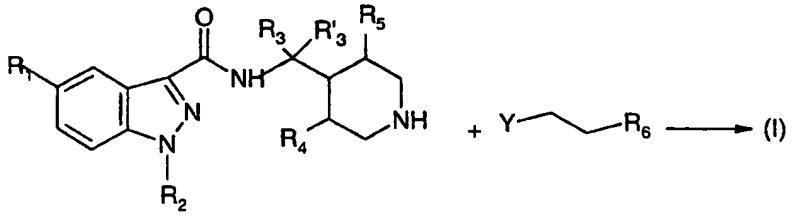
b) de-protecting a compound of the formula (IV) to give a compound of the formula:



(V)

wherein R_1, R_2, R_3, R'_3, R_4 and R_5 have the above mentioned meanings,

c) alkylating a compound of the formula (V) with a compound of the formula (VI) to give a compound of the formula (I) according to the following reaction scheme:



(V) (VI)

wherein

R_1, R_2, R_3, R'_3, R_4, R_5 and R_6 have the above mentioned meanings, and

Y is halogen,

d) optionally forming an acid addition salt of an indazole amide compound of the formula (I) with a pharmaceutically acceptable organic or inorganic acid, or a pharmaceutically acceptable quaternary salt of an indazole amide compound of the formula (I).

Typical examples of protecting groups (P) are benzyloxycarbonyl, benzyl, terbutoxycarbonyl and trimethylsilylethoxycarbonyl.

Step a) is preferably carried out by reacting a compound of the formula (II) with a compound of the formula (III) in which X is chlorine, in

the presence of a suitable diluent and at a temperature of from 0 to 140°C for a period of time of from 0.5 to 20 hours.

Preferably the diluent is aprotic, polar or apolar. Still more preferably, it is aprotic apolar. Examples of suitable aprotic apolar diluents are aromatic hydrocarbons such as, for example, benzene, toluene and xylenes. Examples of suitable aprotic polar diluents are dimethylformamide and dimethylsulphoxide.

Still more preferably, the reaction is performed at a temperature of from 15 to 40°C for a period of time of from 1 to 14 hours.

In turn, step (b) is carried out according to techniques known to the person skilled in the art of the protecting group (Theodora W. Greene and Peter G.M. Wuts, "Protective groups in organic synthesis", pp. 309-406, John Wiley & Sons, Inc., N.Y., 1991). In the case of benzyl and benzyloxycarbonyl, the deprotection of the protecting group is preferably carried out by catalytic hydrogenation. An example of a suitable catalyst is palladium on activated carbon.

Preferably the deprotection is carried out by hydrogenation in the presence of a suitable diluent such as, for example, a low aliphatic alcohol, a low aliphatic acid and mixtures thereof. An example of a preferred diluent is an ethyl alcohol /acetic acid mixture.

Step c) is preferably performed with a compound of the formula (VI), in which Y is chlorine or bromine in the presence of a suitable acceptor of acids such as, for example, alkali carbonates and bicarbonates, low trialkylamines and a suitable diluent such as, for example, aromatic hydrocarbons, dimethylformamide and aliphatic low alcohols.

Typical examples of preferred organic and inorganic acids for forming addition salts of the present invention (step d) are oxalic, maleic, tartaric, methanesulphonic, sulphuric, phosphoric acid, hydrogen bromide and hydrogen chloride.

Methyl iodide is a typical example of a preferred compound forming a pharmaceutically acceptable quaternary salt of the invention.

The preparation of the above mentioned salts comprises addition (step d) of a pharmaceutically acceptable organic or inorganic acid, or of methyl iodide to an indazole amide compound of the formula (I) obtained in step c).

The intermediates of formula (IV) and (V) are new. They are therefore a further object of the present invention.

Alternatively, indazole amide compound of the formula (I) can be prepared by acylation of a suitable 4-aminomethyl piperidine with a compound of the formula (III).

Typical examples of pathological conditions which might benefit from treatment with a pharmaceutical composition according to this invention are all the pathologies which are responsive to treatment with antagonists of 5-HT_4 receptor such as, for example, gastrointestinal disorders associated with high intestinal motility, such as IBS (irritable bowel syndrome), urinary incontinence, and cardiac arrhythmias such as atrial fibrillation.

Preferably, the pharmaceutical compositions of the present invention will be prepared in suitable dosage forms comprising an effective dose of at least one compound of the formula (I) or a pharmaceutically acceptable addition salt thereof or a quaternary salt thereof and at least one pharmaceutically acceptable inert ingredient.

Examples of suitable dosage forms are tablets, capsules, coated tablets, granules, solutions and syrups for oral administration; creams, ointments and medicated adhesive strips for topical administration; suppositories for rectal administration and sterile solutions for injectable, aerosol or ophthalmic administration.

The dosage forms may also contain other conventional ingredients such as stabilizing agents, preservatives, surfactants, buffers, salts for

adjusting the osmotic pressure, emulsifiers, sweeteners, coloring agents, flavoring agents, and the like.

When required by particular therapies, the pharmaceutical composition of the present invention may contain other pharmacologically active ingredients whose concomitant administration is therapeutically useful.

The amount of the compound of formula (I) or of a pharmaceutically acceptable salt thereof may vary within a wide range depending on known factors such as, for example, the type of disease to be treated, the severity of the disease, the patient's body weight, the dosage form, the chosen route of administration, the number of dosage forms administered per day and the effectiveness of the chosen compound of formula (I). However, the optimum amount may be easily and routinely determined by a person skilled in the art.

Typically, the amount of the compound of formula (I) or of a salt thereof in the pharmaceutical composition of this invention will be such as to insure an administered dosage level of from 0.001 to 50 mg/kg/day.

The dosage forms of the pharmaceutical composition according to this invention may be prepared according to methods which are known to the pharmaceutical chemist and comprise mixing, granulation, compression, dissolution, sterilization, and the like.

The following Examples are intended to illustrate the present invention, without limiting it in any way.

EXAMPLE 1

Preparation of 1-isopropyl-1H-3-indazolecarbonyl chloride

(III: R_1 = H, R_2 = C_3H_7)

a) 2-methylpropyl-1-isopropyl-1H-3-indazolecarboxylate

To a solution of 2-methylpropyl-1H-3-indazolecarboxylate (50 g; 0.24 moles) in 1,2-dimethoxy-ethane (300 ml) a solution of isopropyl bromide (27.5 ml; 0.29 moles) in 1,2-dimethoxy-ethane (100 ml) and

KOH (13.5 g; 0.24 moles) was added and the mixture was heated under reflux for 8 hours. After removal of the solvent, the residue was dissolved in toluene (300 ml), the thus obtained solution was washed with 1N NaOH (100 ml), H_2O (2x100 ml) and then dried and concentrated *in vacuum*. The residue was purified from the isomer 2-methylpropyl-2- isopropyl-2H-3- indazolecarboxylate via flash chromatography (eluent, hexane : ethyl acetate = 95:5) to give the title compound (23 g) as an oil.

^{1}H NMR ($CDCl_3$, δ): 1.07 (d, J=7Hz, 6H); 1.66 (d, J=7Hz, 6H); 1.95-2.48 (m, 1H); 4.26 (d, J=7Hz, 2H); 4.96 (hept. J=7Hz, 1H); 7.15-7.70 (m, 3H); 8.03-8.33 (m, 1H).

b) 1-isopropyl-1H-3-indazolecarboxylic acid

A suspension of the compound of the Example 1a) (10 g; 0.04 moles) in 0.75N NaOH (100 ml) was heated under reflux for 12 hours. The solution was then cooled, acidified with 6N HCl (40 ml), the solid precipitate was filtered and recrystallized from 1:1 hexane/ethyl acetate to give the title compound (5.5 g), m.p. 162-3° C (Harada H. et al., "Chem. Pharm. Bull.", 43(11), 1912-1930, 1995).

^{1}H NMR (DMSO, δ); 1.54 (d, J=7Hz, 6H); 5.13 (hept, J=7Hz, 1H); 7.20-7.65 (m, 2H); 7.85 (d, J=8Hz, 1H); 8.14 (d, J=7Hz, 1H); 13.08 (s broad, 1H).

c) 1-isopropyl-1H-3-indazolecarbonyl chloride

Thionyl chloride (4 ml, 0.054 moles) was added to a stirred solution of the compound of the Example 1b) and the mixture was stirred under reflux for 2 hours. After removal of the solvent *in vacuum*, the residue was recrystallized from hexane to give 3.5 g of the title compound, m.p. 63-4° C.

Elemental analysis for $C_{11}H_{11}ClN_2O$	C	H	N
% found:	59.29	5.20	12.76
% calculated:	59.33	4.98	12.58

^{1}H NMR ($CDCl_3$, δ); 1.69 (d, J=7Hz, 6H); 5.00 (hept., J=7Hz, 1H); 7.20-7.70 (m, 3H); 8.03-8.33 (m, 1H).

EXAMPLE 2

Preparation of N3-{[1-(2-phenylethyl)-4-piperidinyl]methyl}-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR 306)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = C_6H_5$)

[1-(2-phenylethyl)-1-piperidinyl]methylamine (3 g; 0.014 moles), prepared as described in EP-A-0 343 307, in toluene (30 ml) was dropped into a suspension of the compound of the Example 1c) (3 g, 0.014 moles) in toluene (30 ml). After 3 hours at room temperature, the solid was filtered, dissolved in H_2O, made basic with 6N NaOH solution and extracted with CH_2Cl_2 (2x200 ml). The solvent was removed by evaporation, the residue was purified on SiO_2 column (eluent, $CHCl_3$: MeOH = 95 : 5) and transformed into the corresponding hydrochloride. The obtained product (2 g) melted at 211-212° C.

Elemental analysis for $C_{25}H_{33}ClN_4O$	C	H	N	Cl^-
% found:	68.13	7.52	12.78	8.03
% calculated:	68.09	7.54	12.70	8.04

^{1}H NMR (DMSO, δ); 1.56 (d, J=7Hz, 6H); 1.50-2.30 (m, 5H); 2.70-3.90 (m, 10H); 5.10 (hept, J=7Hz, 1H); 7.05-7.63 (m, 7H);7.81 (d, J=8Hz, 1H); 8.21 (d, J=8Hz, 1H); 8.47 (t, J=6Hz, 1H); 11.05 (s broad, 1H).

IR (KBr): ν_{co} 1652cm^{-1}.

EXAMPLE 3

Preparation of N3-{ [1-(phenylmethyl)-4-piperidinyl]methyl}-1-isopropyl-1H-3-indazolecarboxamide

(IV: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $P = -CH_2C_6H_5$)

To a stirred solution of 1-isopropyl-1H-3-indazolecarbonyl chloride (52 g; 0.234 moles) in toluene (300 ml) it was added dropwise a solution of [1-(phenylmethyl)-4-piperidinyl]methylamine, prepared as described in WO 94/10174, (47.7 g; 0.234 moles) in toluene (200 ml). After 5 hours, the solvent was removed by evaporation under reduced pressure. The reaction mixture was treated with 2N NaOH, extracted with dichloromethane and concentrated *in vacuum*. The solid residue (95 g) was recrystallized from 7:3 hexane/ethyl acetate to afford the title compound as a white solid (45 g), m.p. 72-74° C.

Elemental analysis for $C_{24}H_{30}N_4O$	C	H	N
% found:	73.78	7.87	14.35
% calculated:	73.81	7.74	14.35

^1H NMR ($CDCl_3$, δ); 1.59 (d, J=7Hz, 6H); 1.10-2.25 (m, 7H); 2.80-3.15 (m, 2H); 3.27-3.60 (m, 4H); 4.86 (hept, J=7Hz, 1H); 7.00-7.60(m, 9H); 8.27-8.52(m, 1H).

IR (KBr): ν_{co} 1641cm^{-1}.

EXAMPLE 4

Preparation of N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide hydrochloride

(V: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$)

A suspension of the product of the Example 3 (28 g; 0.076 moles) in ethyl alcohol (1500 ml) and glacial acetic acid (66 ml) was hydrogenated over 10% Pd-C (13.4 g) at 35 psi for 24 hours. The mixture was filtered and the filtrate concentrated *in vacuum*. The residue was dissolved in water, treated with 5N NaOH and stirred for 2 hours at room temperature. The solid obtained was filtered off (16.6 g) and converted to the corresponding hydrochloride (9.5 g), m.p. 211-214° C (dec.)

Elemental analysis for $C_{17}H_{25}ClN_4O.1/2H_2O$	C	H	N
% found:	58.82	7.68	16.36
% calculated:	59.03	7.58	16.20

^{1}H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.31-2.18 (m, 5H); 2.58-3.64 (m, 7H); 5.09 (hept, J=7Hz, 1H); 7.12-7.60 (m, 2H); 7.80 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.41 (t, J=6Hz, 1H); 8.82-9.60 (m, 2H).

IR (KBr): ν_{co} 1658 cm^{-1}.

EXAMPLE 5

Preparation of N3-{[1-(4-phenylbutyl)-4-piperidinyl]methyl}-1-isopropyl-1H-3-indazolecarboxamide oxalate (AFR603)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = -CH_2CH_2C_6H_5$)

To a stirred suspension of the product of Example 4 as free base (5.27 g; 15.6 mmoles) in ethyl alcohol (20 ml), K_2CO_3 (6.5 g; 50 mmoles) and 4-phenylbromobutane ("Braun", B-44, 2872, 1911) (3,6 g, 17.1 mmoles) were added. The reaction mixture was stirred at reflux for 10 hours. After removal of the solvent, the residue was partitioned between ethyl acetate and 1N HCl. The water phase was made basic with 2N NaOH, extracted with ethyl acetate and concentrated *in vacuum*. The solid was converted to the corresponding oxalate salt (2 g), m.p. 154-155° C.

Elemental analysis for $C_{29}H_{38}N_4O_5.1/2H_2O$	C	H	N
% found:	65.87	7.47	10.62
% calculated:	65.52	7.39	10.54

^{1}H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.31-2.18 (m, 5H); 2.30-3.64 (m, 14H); 5.08 (hept, J=7Hz, 1H); 7.12-7.60 (m, 7H); 7.80 (d, J=8Hz, 1H); 8.19 (d, J=8Hz, 1H); 8.41 (t, J=6Hz, 1H).

EXAMPLE 6

Preparation of N3-{[1-(2-cyclohexylethyl)-4-piperidinyl]methyl}-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR604)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = C_6H_{11}$)

Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (4.42 g) and (2-bromoethyl)-cyclohexane ("J.A.C.S.", 48, 1089-1093, 1926) (4.63 g) gave the title compound (2.5 g), m.p. 244-246° C (dec.)

Elemental analysis for $C_{25}H_{39}N_4O.1/2\ H_2O$	C	H	N	Cl^-
% found:	65.51	9.05	12.57	7.89
% calculated:	65.83	8.84	12.28	7.77

^1H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 0.68-2.18 (m, 17H); 2.63-3.70 (m, 10H); 5.09 (hept, J=7Hz, 1H); 7.12-7.60 (m, 2H); 7.80 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.41 (t, J=6Hz, 1H); 10.70 (s broad 1H).

IR (KBr): ν_{co} 1656 cm^{-1}.

EXAMPLE 7

Preparation of N3-({1-[3-(dimethylamino)propyl]-4-piperidinyl}methyl)-1-isopropyl-1H-3-indazolecarboxamide dimaleate (AFR606)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = -CH_2NC_2H_6$)

Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (3 g) and N-(3-chloropropyl)-N, N-dimethylamine hydrochloride (580 mg) gave the title compound (950 mg), m.p. 155-156° C.

Elemental analysis for $C_{30}H_{43}N_5O_9.1/2H_2O$	C	H	N
% found:	57.83	7.01	11.11
% calculated:	57.50	7.08	11.18

^{1}H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.68-2.28 (m, 7H); 2.81 (s, 6H); 2.75-3.75 (m, 11H); 5.09 (hept, J=7Hz, 1H); 6.09 (s, 4H); 7.12-7.60 (m, 2H); 7.81 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.45 (t, J=6Hz, 1H).

EXAMPLE 8

Preparation of N3-({1-[2-(4-morpholinyl)ethyl]-4-piperidinyl}methyl)-1-isopropyl-1H-3-indazolecarboxamide dihydrochloride (AFR607)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = C_4H_4NO$)

Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (3 g) and 4-(2-chloroethyl)-morpholine (3.42 g) gave the title compound (3.2 g), m.p. 266-267° C (dec.)

Elemental analysis for $C_{23}H_{37}Cl_2N_5O_2.1/2\ H_2O$	C	H	N	Cl^-
% found:	55.74	7.61	13.96	14.12
% calculated:	55.75	7.73	14.13	14.31

^{1}H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.30-2.25 (m, 5H); 2.75-4.30 (m, 19H); 5.09 (hept, J=7Hz, 1H); 7.12-7.60 (m, 2H); 7.81 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.45 (t, J=6Hz, 1H); 10.80 (s broad, 1H); 10.60 (s broad, 1H).

IR (KBr): ν_{co} 1652 cm^{-1}.

EXAMPLE 9

Preparation of N3-[(1-{ 2-[(methylsulphonyl)amino]ethyl}4-piperidinyl)methyl]-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR703)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = CH_3SO_2NH$-)

Following the procedure of Example 5, N3-(4-piperidinylmethyl)-1-isopropyl-1H-3-indazolecarboxamide (5 g) N-(2-bromoethyl)-methane sulphonamide (WO 93/18036) (3 g) gave the title compound (1.5 g), m.p. 186-187° C (dec.)

Elemental analysis for $C_{20}H_{32}ClN_5O_3S$	C	H	N	S	Cl^-
% found:	52.15	7.22	15.30	6.98	7.77
% calculated:	52.45	7.04	15.29	7.00	7.74

^1H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.40-2.30 (m, 5H); 3.00 (s, 3H); 2.75-3.80 (m, 10H); 5.09 (hept, J=7Hz, 1H); 7.12-7.70 (m, 3H); 7.80 (d, J=8Hz, 1H); 8.20 (d, J=8Hz, 1H); 8.45 (t, J=6Hz, 1H); 10.73 (s broad, 1H).

IR (KBr): ν_{co} 1651cm^{-1}.

EXAMPLE 10

Preparation of N3-({1-[2-(2-pyridinyl)ethyl] 4-piperidinyl}methyl)-1-isopropyl-1H-3-indazolecarboxamide hydrochloride (AFR605)

(I: $R_1 = R_3 = R'_3 = R_4 = R_5 = H$, $R_2 = C_3H_7$, $R_6 = C_5H_4N$)

To a stirred suspension of the product of Example 4 as free base (10 g; 33.3 mmoles), 2-vinylpyridine (3.6 g; 34 mmoles), glacial acetic acid (2 ml) and water (2.5 ml) were added. After 16 hours at 95° C, the reaction mixture was made basic with 2N NaOH, extracted with ethyl acetate and concentrated *in vacuum*. The residue was purified by flash silica-gel chromatography with $CHCl_3$:MeOH = 97 : 3 as eluent to yield a solid which was converted to hydrochloride salt (5 g), m.p. 122-123° C (dec.)

Elemental analysis for $C_{24}H_{32}ClN_5O.H_2O$	C	H	N	Cl^-
% found:	62.80	7.42	15.18	7.78
% calculated:	62.66	7.45	15.22	7.71

^1H NMR (DMSO, δ); 1.55 (d, J=7Hz, 6H); 1.68-2.30 (m, 5H); 2.80-3.78 (m, 12H); 5.10 (hept, J=7Hz, 1H); 7.12-7.60 (m, 4H); 7.68-8.00 (m, 2H); 8.21 (d, J=7Hz, 1H); 8.33-8.70 (m, 2H); 11.05 (s broad, 1H).

IR (KBr): ν_{co} 1644 cm^{-1}.

TEST 1

Antagonistic Action on 5-HT_4 Receptor

The antagonistic action of the compounds of the formula (I) was evaluated by testing the influence of the compound under evaluation on serotonin-induced relaxation of rat oesophageal tunica pre-contracted with carbachol according to the method described by J.D. Gale et al. in "Br. J. Pharmacol.", 111, 332-338, (1994).

All the tested compounds of the invention showed a $pA_2 > 8$. The specific values for AFR 603, AFR 604, AFR 605 and AFR 306 are shown Table 1 below.

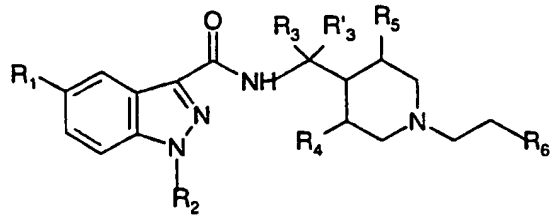
Table 1

Compound	pA_2	s.e.
AFR 603	9.12	1.42
AFR 604	8.19	0.99
AFR 605	10.8	1.90
AFR 306	9.36	0.38

s.e. = standard error

CLAIMS

1. A compound having the general formula



(I)

wherein:

R_1 is hydrogen;

R_2 is isopropyl;

R_3 and R'_3 are hydrogen;

R_4 and R_5 are hydrogen;

R_6 is selected from the group comprising C_{1-3} alkyl, C_{3-7} cycloalkyl, heterocyclic ring having from 5 to 6 members where 1 to 4 members are heteroatoms, the same or different from each other, selected from the group comprising N, O and S, dimethylamino C_{1-3} alkyl, methoxy C_{1-3} alkyl, N-phenyl amide, aminosulphonylmethyl, dihydroxy C_{2-3} alkyl, aryl, aryl substituted by at least a group selected from halogen and hydroxy, aryl C_{1-3} alkyl;

acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

2. A compound according to claim 1, characterized in that aryl is selected from the group comprising phenyl, naphthyl and biphenyl.

3. A compound according to claim 1, characterized in that heterocyclic rings are thienyl, furanyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, furazanyl,

pyrrolinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, morpholinyl, triazinyl, thiazolyl, tetrazolyl and thiadiazolyl.

4. A compound according to claim 1, characterized in that R_6 is selected from the group comprising cyclopropyl, cyclohexyl, pyridinyl, tetrazolyl, morpholinyl, methoxymethyl, methoxypropyl, phenyl, chlorophenyl, bromophenyl, hydroxyphenyl, phenethyl, dimethylaminomethyl, and aminosulphonylmethyl.

5. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is phenyl.

6. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is phenethyl.

7. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is cyclohexyl.

8. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is pyridinyl.

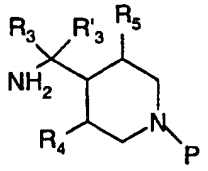
9. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is dimethylaminomethyl.

10. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is morpholinyl.

11. A compound according to claim 1, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and R_6 is aminosulphonylmethyl.

12. A process for preparing a compound of the formula (I), acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof, comprising:

a) acylating a 4-aminomethyl piperidine of the formula:



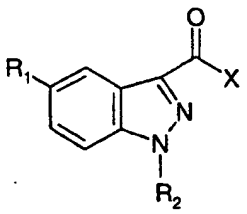
(II)

wherein

R_3, R'_3, R_4 and R_5 have the above mentioned meanings, and

P is a suitable protecting group;

by means of a 1-alkyl-indazole-3-carboxylic acid halide of the formula:



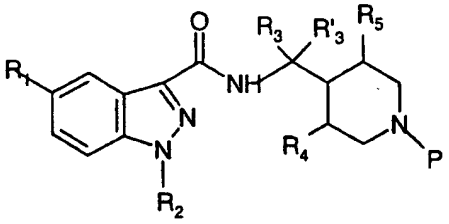
(III)

wherein

R_1 and R_2 have the above mentioned meanings, and

X is halogen,

to give a compound of the formula:

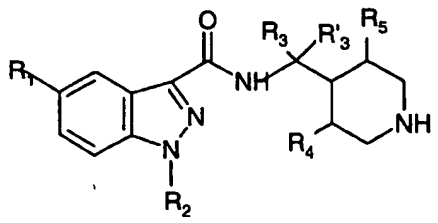


(IV)

wherein

R_1, R_2, R_3, R'_3, R_4, R_5 and P have the above mentioned meanings,

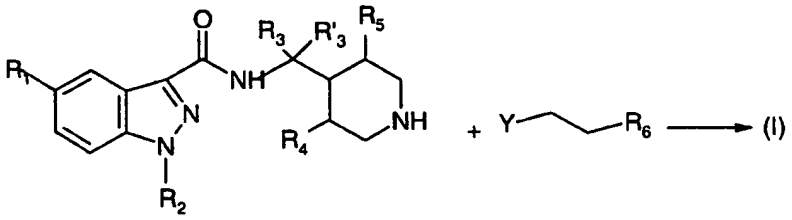
b) de-protecting a compound of the formula (IV) to give a compound of the formula:



(V)

wherein R_1, R_2, R_3, R'_3, R_4 and R_5 have the above mentioned meanings,

c) alkylating a compound of the formula (V) with a compound of the formula (VI) to give a compound of the formula (I) according to the following reaction scheme:



(V) (VI)

wherein

R_1, R_2, R_3, R'_3, R_4, R_5 and R_6 have the above mentioned meanings, and

Y is halogen,

d) optionally forming an acid addition salt of an indazole amide compound of the formula (I) with a pharmaceutically acceptable organic or inorganic acid, or a pharmaceutically acceptable quaternary salt of an indazole amide compound of the formula (I).

13. A process according to claim 12, characterized in that P is selected from the group comprising benzyloxycarbonyl, benzyl, terbutoxycarbonyl, trimethylsilylethoxycarbonyl.

14. A process according to claims 12 or 13, characterized in that step a) is carried out by reacting a compound of the formula (II) with a

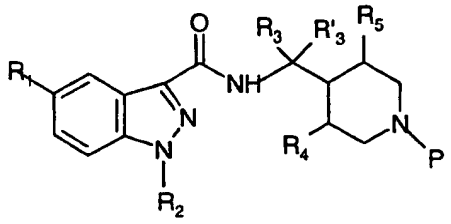
compound of the formula (III) in which X is chlorine, in the presence of a diluent and at a temperature of from 0 to 140°C for a period of time of from 0.5 to 20 hours.

15. A process according to claim 13, characterized in that when P is benzyl or benzyloxycarbonyl, step b) is carried out by catalytic hydrogenation.

16. A process according to any of the preceding claims from 12 to 14, characterized in that when, in a compound of the formula (VI), Y is chlorine or bromine, step c) is performed in the presence of an acceptor of acids and in the presence of a diluent.

17. A process according to claim 12, characterized in that methyliodide forms a pharmaceutically acceptable quaternary salt of a compound of formula (I), step d).

18. An intermediate compound having the general formula:



(IV)

wherein

R_1 is hydrogen;

R_2 is isopropyl;

R_3 and R'_3 are hydrogen;

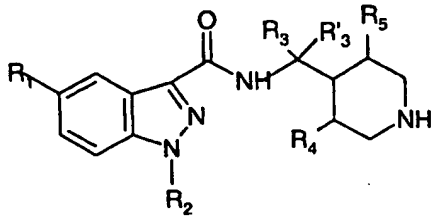
R_4 and R_5 are hydrogen; and

P is a protecting group.

19. A compound according to claim 18, characterized in that P is selected from the group comprising benzyloxycarbonyl, benzyl, terbutoxycarbonyl, trimethylsilylethoxycarbonyl.

20. A compound according to claim 18, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen, R_2 is isopropyl and P is benzyl.

21. An intermediate compound having the general formula:



(V)

wherein

R_1 is hydrogen;

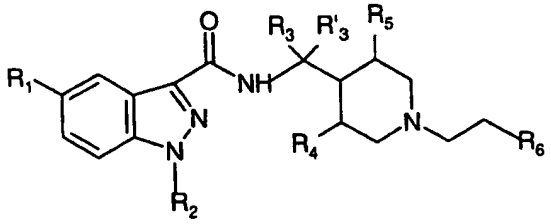
R_2 is isopropyl;

R_3 and R'_3 are hydrogen;

R_4 and R_5 are hydrogen.

22. A compound according to claim 17, characterized in that R_1, R_3, R'_3, R_4 and R_5 are hydrogen and R_2 is isopropyl.

23. A pharmaceutical composition, characterized in that the said composition comprises an effective dose of at least one compound of the formula:



(I)

wherein

R_1 is hydrogen;

R_2 is isopropyl;

R_3 and R'_3 are hydrogen;

R_4 and R_5 are hydrogen;

R_6 is selected from the group comprising C_{1-3} alkyl, C_{3-7} cycloalkyl, heterocyclic ring having from 5 to 6 members where 1 to 3 members are heteroatoms, the same or different from each other, selected from the group comprising N, O and S, dimethylamino C_{1-3} alkyl, methoxy C_{1-3} alkyl, N-phenyl amide, aminosulphonylmethyl, dihydroxy C_{2-3} alkyl, aryl, aryl substituted by at least a group selected from halogen and hydroxy, aryl C_{1-3} alkyl;

acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

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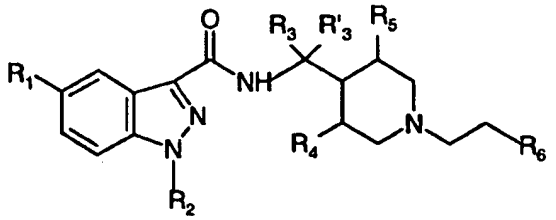
(54) Title: INDAZOLE AMIDE COMPOUNDS AS SEROTONINERGIC AGENTS



(I)

(57) Abstract

A compound having general formula (I) wherein R_1, R_2, R_3, R'_3, R_4, R_5 and R_6 have the meanings stated in the description, acid addition salts thereof with pharmaceutically acceptable organic and inorganic acids and pharmaceutically acceptable quaternary salts thereof.

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INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/EP 98/02129

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 A61K31/415

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 38420 A (NISSHIN FLOUR MILLING CO) 5 December 1996 see abstract see page 64 - page 65; example 7 see page 73; example 18 see page 75; example 21	1-11,18, 21,23
P,X	-& EP 0 829 474 A (NISSHIN FLOUR MILLING CO) 18 March 1998 see page 49 - page 50; example 7 see page 56; example 18 see page 57 - page 58; example 21 see claims 1,10,16-21	
X	WO 93 03725 A (SMITHKLINE BEECHAM PLC) 4 March 1993 see page 2, line 1 - page 3, line 30 see page 32; example 10 see page 46 - page 47; example 39	1-11,18, 21,23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 October 1998	14/10/1998

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate. of the relevant passages	Relevant to claim No.
A	EP 0 732 333 A (LILLY CO ELI) 18 September 1996 see the whole document ---	1,23
A	EP 0 501 322 A (GLAXO GROUP LTD) 2 September 1992 see the whole document -----	1,23

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inte nal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9638420 A	05-12-1996	CA 2222532 A	05-12-1996
		EP 0829474 A	18-03-1998
WO 9303725 A	04-03-1993	AU 2435092 A	16-03-1993
		AU 5194496 A	18-07-1996
		CA 2116024 A	04-03-1993
		EP 0600955 A	15-06-1994
		JP 6510283 T	17-11-1994
		MX 9204786 A	01-04-1993
		NZ 243993 A	26-10-1994
		PT 100785 A	29-04-1994
		ZA 9206208 A	24-05-1993
		AP 373 A	07-12-1994
		AU 668102 B	26-04-1996
		AU 2541892 A	05-04-1993
		AU 691430 B	14-05-1998
		AU 6073596 A	03-10-1996
		BR 9206599 A	08-11-1994
		CA 2118812 A	18-03-1993
		CN 1073173 A	16-06-1993
		CZ 9400560 A	13-07-1994
		EP 0604494 A	06-07-1994
		FI 941178 A	11-03-1994
		WO 9305038 A	18-03-1993
		HU 70154 A	28-09-1995
		JP 6510537 T	24-11-1994
		MX 9205204 A	31-01-1994
		NO 940874 A	11-03-1994
		NZ 244282 A	28-08-1995
		PT 100855 A	30-11-1993
		SG 49153 A	18-05-1998
		SK 30294 A	07-12-1994
		US 5580885 A	03-12-1996
EP 0732333 A	18-09-1996	US 5654320 A	05-08-1997
		AU 6894896 A	18-11-1996
		CA 2215359 A	31-10-1996
		CN 1183041 A	27-05-1998
		NO 974221 A	27-10-1997
		PL 322362 A	19-01-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ›nal Application No
PCT/EP 98/02129

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0732333 A		SK 124297 A	04-02-1998
		WO 9633713 A	31-10-1996
		US 5798367 A	25-08-1998
EP 0501322 A	02-09-1992	AT 142205 T	15-09-1996
		AU 645402 B	13-01-1994
		AU 1209492 A	15-09-1992
		CA 2105179 A	26-08-1992
		DE 69213276 D	10-10-1996
		DE 69213276 T	23-01-1997
		WO 9214727 A	03-09-1992
		ES 2091963 T	16-11-1996
		FI 933697 A	23-08-1993
		HU 65486 A	28-06-1994
		IL 101042 A	18-06-1996
		JP 6505238 T	16-06-1994
		MX 9200762 A	01-08-1992